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Synthesis of the Azepinobisindole Alkaloid Iheyamine A Enabled by a Cross-Mannich Reaction

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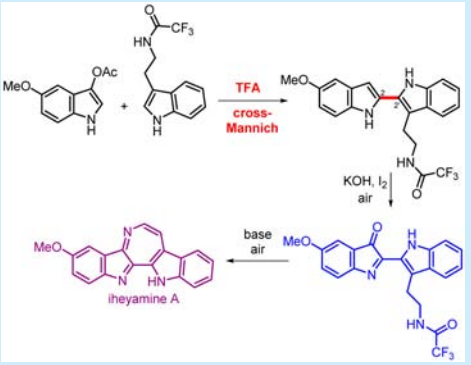
Supporting Information

ABSTRACT: The total synthesis of the azepinobisindole alkaloid iheyamine A is described. The successful strategy hinged on an intermolecular cross-Mannich reaction between 5-methoxy-3-acetoxyindole and a protected tryptamine to access an unsymmetrical 2,2′-bisindole, which was subsequently converted into iheyamine A via a deep-blue 3-indolone intermediate. VT ^{1}H NMR infers that iheyamine A exists as a mixture of tautomers that undergo intermediate chemical exchange on the NMR time scale. The intermolecular cross-Mannich reaction described herein is a viable alternative to metal-catalyzed cross-coupling strategies commonly employed to access 2,2′-bisindoles.



Iheyamines A (**1**) and B (**2**) are purple alkaloids isolated from the ascidian *Polycitorella* sp. collected off Iheya Island, Okinawa.[1] The iheyamines possess an intriguing azepinobisindole framework also present in the recently isolated natural product (−)-trigonoliimine C (**3**)[2] (Figure 1). Despite being

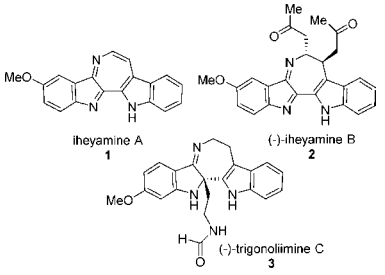
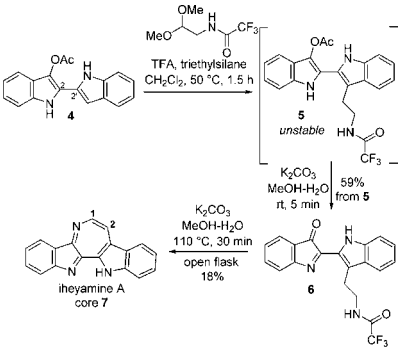


Figure 1. Azepinobisindole alkaloids.

isolated in 1999, Bremner's attempted biomimetic synthesis of an iheyamine A model system remains the only report detailing synthetic efforts toward these alkaloids.[3] The fascinating heteroaromatic structure of these natural products combined with our ongoing interest in the synthesis of bisindole alkaloids[4] prompted initiation of a synthetic program targeting iheyamine A.

Our preliminary focus was to develop a route to the unique azepinobisindole core of iheyamine A that could subsequently be applied to the natural product itself. Our overall strategy was to install the 2,2′-bisindole bond prior to assembly of the central azepine ring. Accordingly, the indigo-derived acetoxybisindole **4**[5] was deemed a good substrate upon which to evaluate the viability of this approach (Scheme 1). Installation of a tryptamine side chain onto **4** by reductive alkylation[6] appeared to proceed well by

Scheme 1. Synthesis of the Iheyamine A Core 7



TLC to give **5**,[7] but during workup and purification a dark purple compound quickly formed, identified as the indolone **6**[8] arising from **5** undergoing hydrolysis and oxidation. The acetoxybisindole **4** was subsequently converted to **6** in good yield using an optimized one-pot procedure. Upon treating indolone **6** with potassium carbonate in aqueous methanol at reflux, trifluoroacetamide hydrolysis, cyclization, and aromatization all occurred in one pot to give **7**, the azepinobisindole core of iheyamine A.

The structure of **7** was confirmed by the presence of the distinctive downfield chemical shifts of the azepine protons in the ^{1}H NMR spectrum.[9] With the successful synthesis of the azepinobisindole core **7**, attention turned to the natural product itself. Basing the proposed synthesis of iheyamine A (**1**) on the successful model study, the unsymmetrical 2,2′-bisindole **8** was

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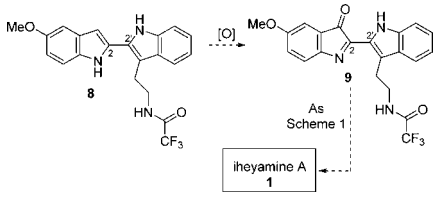
identified as a key intermediate. Oxidation of **8** to the indolone **9** followed by intramolecular cyclization−aromatization would complete the synthesis of iheyamine A (**1**) (Scheme 2). The

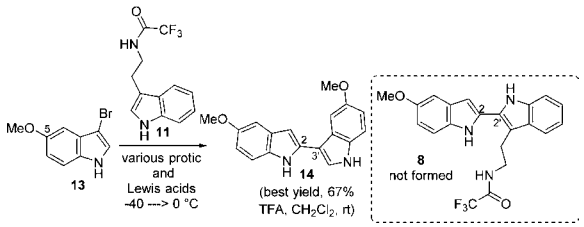
Scheme 2. Proposed Synthesis of Iheyamine A (1) from Unsymmetrical 2,2′-Bisindole 8



synthesis of unsymmetrical 2,2′-bisindoles (i.e., **8**) is typically accomplished by metal-mediated cross-coupling,[2b,c,10] heterocyclization reactions,[11,12] or the base-mediated coupling of indole triflones.[13] 2,2′-Bisindoles can also be desymmetrized upon reaction with an electrophile at C3.[14] We were keen to develop a new method to assemble the 2,2′-bisindole **8**, and of particular interest was the well-established acid-catalyzed homodimerization of 3-substituted indoles, a reaction that follows a Mannich-type pathway to give 2-(indolin-2-yl)-indoles[15] that are readily dehydrogenated to give symmetrical 2,2′-bisindoles (Scheme 3, **A**).[16] This reaction is currently limited to symmetrical products, and predictably, using two different indoles in this process leads to a mixture of homo- and heterodimers as observed during a recent biomimetic synthesis of homofascaplysin C.[17,18] The utility of this reaction would be greatly enhanced if it could be used to access unsymmetrical 2,2′-bisindoles such as the target **8**. Toward this end, an intriguing report from 1981 describes the Lewis acid-mediated cross-Mannich reaction between 3-alkyl-2-chloroindoles and 3-alkylindoles to give 3,3′-dialkyl-2,2′-bisindoles as the sole products, eliminating the need for a separate dehydrogenation step due to the loss of HCl after the [1,2]-shift (Scheme 3, **B**).[19] Given that both substrates are 3-alkylindoles in this instance, the [1,2]-shift is favored and the 2,2′-bisindoles result. However, using an indole with an unsubstituted C3-site (R^2 or R^4 = H) in this reaction would lead to a 2,3′-bisindole, and thus, this methodology is not amenable to the synthesis of target **8**. Using this literature example as a guide, it was considered that an indole **10** bearing a heteroatom substituent (X) at C3 would undergo preferential protonation,[20] initiating a cross-Mannich reaction with tryptamine **11** to give intermediate **12**. A [1,2]-shift followed by loss of HX/H^+ would give the desired 2,2′-bisindole **8** possessing the vacant C3 site (Scheme 3, **C**).

The initial idea was to place a bromide substituent at C3 and attempt the cross-Mannich reaction with tryptamine **11**.[21] Accordingly, 3-bromo-5-methoxyindole **13**[22] and tryptamine **11**[23] were subjected to variety of acidic conditions, but only the 2,3′-bisindole **14**[24] was ever isolated, with none of the desired 2,2′-bisindole **8** observed (Scheme 4). The propensity for

Scheme 4. Cross-Mannich Reaction Fails with 5-Methoxy-3-bromoindole (13)



homodimeric 2,3′-bisindole **14** to form can be attributed to the indole **10** reacting faster in the Mannich reaction than tryptamine **11**. Evidently, for the cross-Mannich reaction to succeed, the nucleophilicity of the indole coupling partner had to be reduced so that the tryptamine **11** could react in the initial C−C bond-forming step. This was deemed achievable by replacing bromide with the slightly stronger electron-withdrawing acetoxy group, a switch that would reduce the nucleophilicity of the indole but is unlikely to compromise the final elimination step (Scheme 3, **C**). As such, 5-methoxy-3-acetoxyindole **15** was the next candidate for the cross-Mannich reaction. Upon addition of **15**[25] to a solution containing an equimolar amount of tryptamine **11** in TFA at 0 °C (Table 1, entry 1), the 3-acetoxyindole **15** was

Scheme 3. Synthesis of 2,2′-Bisindoles Using the Mannich Reaction

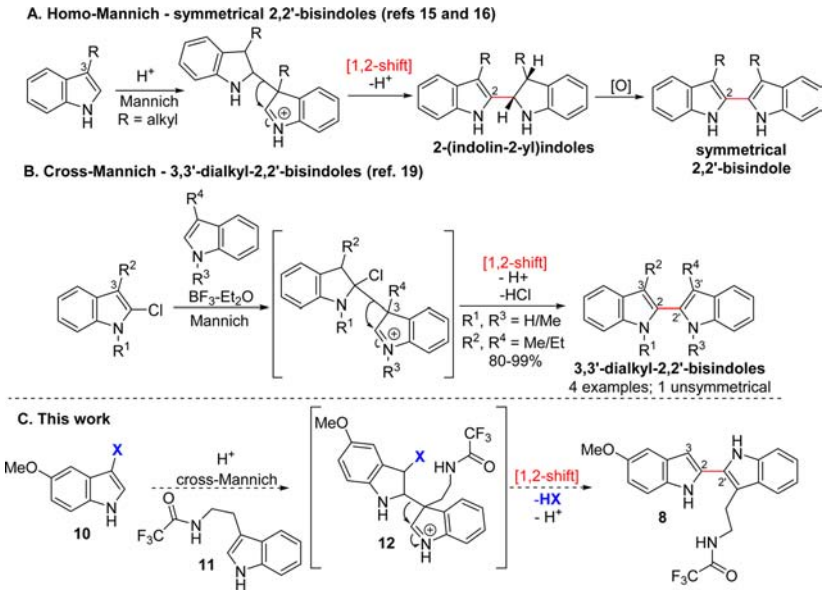


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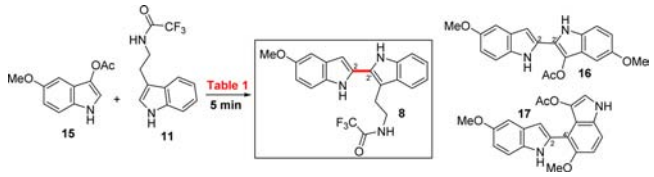
Table 1. Synthesis of 2,2′-Bisindole 8 by Cross-Mannich Reaction



entry	ratio **15**:**11**[a]	solvent	acid	temp (°C)	yield of **8** (%)	ratio **8**:[**16** + **17**] (by mass)
1	1:1	none	TFA	0	50	2.5:1
2	1:2	none	TFA	0	60	4.8:1
3	2:1	none	TFA	0	74	1.6:1
4	**3:1**	**none**	**TFA**	**0**	**93**	**2.0:1**
5	3:1	CH_2Cl_2	TFA	0	~70 (impure)[b,c]	~1.6:1
6	3:1	CH_2Cl_2	TFA	−10	no reaction[d]	
7	3:1	THF	TCA	0 → 40	degradation	
8	3:1	dioxane	HCl	0	degradation of **15**	
9	3:1	CH_2Cl_2	Lewis acids	−40 → 0	0	complex mixtures[e]

[a]In all reactions, a solution of acetoxyindole **15** in a *minimal* amount of dichloromethane was added dropwise to a stirred solution of tryptamine **11** in the solvent/acid. [b]2,2′-Bisindole **8** was inseparable from tryptamine **11**. [c]Using TFA in a variety of alternative solvents (1,2-DCE, THF, $MeNO_2$, MeCN, toluene) gave poor yields of predominantly homodimeric products. [d]TFA freezes at −15 °C, so CH_2Cl_2 was added when the reaction was run below 0 °C. [e]$TiCl_4$, $BF_3{\cdot}Et_2O$, and $AlCl_3$ all gave a complex mixture of **16** and **17**, alongside several unidentified trimers/oligomers.

rapidly consumed (TLC analysis, <1 min), and the desired 2,2′-bisindole **8** was formed in 50% yield, the gross structure of which was confirmed by detailed NMR analyses (Figure 2).[9] Some

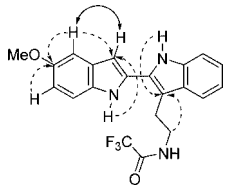
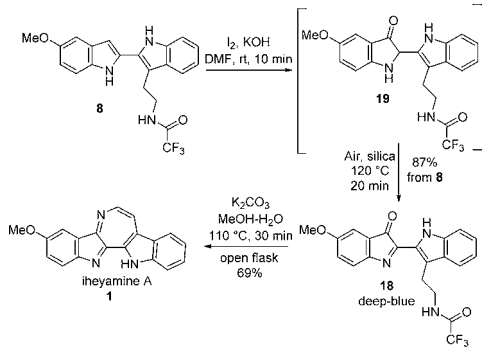


Figure 2. Key NOESY (double headed arrow) and $^1H-^{13}C$ HMBC (dotted arrows) correlations for 2,2′-bisindole **8**.

homodimerization was also evident in this reaction, the products of which were identified as 2,2′-bisindole **16** and 2,4′-bisindole **17**. Although performing the reaction with an excess of tryptamine **11** gave a better yield of **8** and significantly reduced the amount of homodimers formed (entry 2), purification of the 2,2′-bisindole **8** was extremely cumbersome as it coeluted with the residual tryptamine **11** remaining in the reaction.

Employing an excess of the indole **15** gave a good yield of the 2,2′-bisindole **8**, and although the quantity of homodimers increased, purification of **8** was facile (entry 3). Increasing the amount of acetoxyindole **15** to 3 equiv gave reproducibly excellent yields of the 2,2′-bisindole **8** (entry 4). A solvent screen revealed that the cross-Mannich reaction is remarkably intolerant of most solvents; the reaction does proceed when dichloromethane is used, but purification of **8** is cumbersome and homodimerization still apparent (entry 5). Reducing the reaction temperature in an effort to diminish homodimerization was met with failure, with no reaction occurring below 0 °C (entry 6). Replacing TFA with trichloroacetic acid (entry 7) and hydrochloric acid (entry 8) resulted in a poor outcome, whereas various Lewis acids promoted the formation of homodimers, trimers, and oligomers (entry 9). With the 2,2′-bisindole **8** in hand, attention turned to the oxidation of the vacant C3 site and completing the first synthesis of iheyamine A (**1**) (Scheme 5). Several oxidants known to convert indoles into 3-oxindoles served only to degrade **8**, including Cu(I)[26] and Cu(II)[27] salts, NBS,[28] and $VO(acac)_2$.[29]

Scheme 5. Total Synthesis of Iheyamine A (1)



Given the difficulties[30] associated with the oxidation of **8**, we planned to acetoxylate the C3 site (via the 3-iodoindole)[31] and convert the resulting 3-acetoxyindole to the desired indolone **18** according to the model study (Scheme 1). Serendipitously, upon subjecting **8** to potassium hydroxide and iodine in DMF (conditions frequently used to iodinate indoles[32]), a product was formed that slowly converted to the deep-blue indolone **18** upon workup and purification. This interesting outcome can be explained by the initial iodonium ion undergoing attack at C3 by hydroxide[33] followed by elimination of HI to give indoxyl **19**, which readily oxidizes to the indolone **18**. By simply adding silica gel and stirring under air once **8** was consumed (by TLC), the presumed indoxyl **19** was readily converted to the indolone **18** in excellent yield over two steps from **8**. The pivotal deprotection−cyclization−aromatization sequence proceeded well to give iheyamine A (**1**), the gross structure of which was confirmed by detailed spectroscopic analysis, which was identical in all aspects to the isolation report.[1] Finally, we sought to confirm if iheyamine A (**1**) exists as the tautomeric form depicted herein.[1] However, the absence of an N−H signal in the ^1H NMR of both the free base and TFA salt of iheyamine A[34] infers that in solution iheyamine A exists as a mixture of tautomers that undergo

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intermediate chemical exchange on the NMR time scale, even at −30 °C.[9,35]

To conclude, the synthesis of the core structure **7** from indigo laid the foundations for the first total synthesis of iheyamine A (**1**), a unique azepinobisindole alkaloid. The success of the synthesis hinged on development of a novel cross-Mannich reaction between acetoxyindole **15** and the tryptamine **11** to give the unsymmetrical 2,2′-bisindole **8**. The serendipitous conversion of **8** into the deep-blue indolone **18** followed by base-mediated intramolecular condensation and aromatization gave iheyamine A (**1**), the spectroscopic data for which were in full agreement with the isolation report.[1,9] The novel intermolecular cross-Mannich reaction described herein offers an efficient alternative to commonly employed metal-catalyzed cross-coupling strategies and should enable the rapid synthesis of other alkaloids that possess a 2,2′-bisindole bond, such as cladoniamide G.[36]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02798.

Full experimental procedures and NMR spectra of all novel compounds (PDF)

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Notes

The authors declare no competing financial interest.

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